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## APPENDIA - SPECIFICATION/CLAIM AMENDMENTS INCLUDING NOTATIONS TO INDICATE CHANGES MADE

Applicant(s):James B. McCarthy et al. Serial No.:09/937,076 Confirmation No.: 4527 Filed: September 19, 2001

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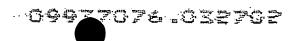
For:METHODS OF USE OF \$1-INTEGRIN INHIBITORS

Amendments to the following are indicated by underlining what has been added and bracketing what has been deleted. Additionally, all amendments have been shaded.

## In the Specification

The paragraph beginning at page 35, line 2, has been amended as follows:

Transient cerebral ischemia and associated brain injury may be mediated by several factors, including inflammatory processes (Hallenbeck et al., Stroke, 17, 246-253 (1986)). Leukocyte infiltration into ischemic tissue is a pathophysiological response, which often further aggravates ischemic injury by attenuating microvascular blood flow, and releasing chemical mediators such as free oxygen radicals (Kochanek et al., Stroke, 23, 1367-1379 (1992); and Matsuo et al., J. Cereb. Blood Flow Met., 15, 941-947 (1995)). Cell adhesion molecules play important roles in leukocyte-endothelial interactions: the selectins (Lasky, Science, 258, 964-969 (1992)), the integrins, and the immunoglobulin superfamilies (Springer, Nature, 346, 425-434 (1990)). Integrins which contain  $\beta_1$  subunits usually are associated with mediating adhesion to extracellular matrix constituents (Springer, Nature, 346, 425-434 (1990)) whereas  $\beta_2$  integrins are largely involved in cell-cell interactions. One of these extracellular matrix macromolecules is fibronectin, which is found in plasma, cell matrix, and on the cell surface. These molecules can support leukocyte adhesion to endothelial cells (Akiyama et al., Adv. Enzymol., [57]59, 1-57 (1987)).



## APPENDIX A - SPECIFICATION/CLAIM AMENDMENTS INCLUDING NOTATIONS TO INDICATE CHANGES MADE

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METHODS OF USE OF \$1-INTEGRIN INHIBITORS

The paragraph beginning at page 35, line 18, has been amended as follows:

Fibronectin possesses multiple domains recognized by integrins, including arginyl-glycyl-aspartic acid (RGD). The latter interacts selectively with α5β1 integrin, and the alternately spliced connecting segment domain (CS-1) which is recognized selectively by α4β1 integrin (Akiyama et al., Adv. Enzymol., [57] 59. 1-57 (1987); and Guan et al., Cell, 60, 53-61 (1990)). Over the last few years several novel (nonRGD/nonCS-1) bioactive peptides from fibronectin that: a) antagonize leukocyte adhesion of activated lymphocytes and monocytes in vitro when used as soluble antagonists and b) show efficacy for improved outcomes in several in vivo animal models of chronic and acute inflammation when administered intravenously. These models include bacterial cell wall-induced arthritis in rats, models of autoimmune disease such as TGF-β -/- mice, and reperfusion injury in rat transient cerebral ischemia and in rabbit burn models (Hines et al., Proc. Natl. Acad. Sci., USA, 91, 5187-5191 (1994); Wahl et al., J. Clin. Invest., 94, 655-662 (1994); and unpublished data).